

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20- 838**

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA 20-838

ATACAND

Candesartan Cilexetil tablets (4, 8, 16 mg)

Sponsor: Astra Merck

submission date: 4/30/97, 6/27/97, 7/15/97, 7/29/97, (2) 11/18/97, 12/8/97, (2) 12/10/97

Reviewer: Ahmed El-Tahtawy, Ph.D.

Category: 1S

SYNOPSIS

Candesartan cilexetil is a new, potent, long-acting, selective angiotensin II type I receptor (AT1) antagonist. Esterification of candesartan yields candesartan cilexetil, an inactive prodrug with markedly improved oral bioavailability compared to candesartan. Candesartan cilexetil is rapidly and completely hydrolyzed to the active drug during absorption from the gastrointestinal tract.

Candesartan is mainly excreted unchanged in urine (33%), and feces (67%). It undergoes minor hepatic metabolism which forms an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. The pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. The peak serum concentration (C_{max}) is reached after 3-4 hours. Food with a high-fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once daily administration. There is no difference in the pharmacokinetics of candesartan between male and female subjects. In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. The AUC and C_{max} were approximately double in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) compared to patients with normal kidney function. No differences in the pharmacokinetics of candesartan were observed in patients with mild to moderate chronic liver disease. Candesartan is not likely to influence the metabolism of other drugs, or be influenced by other drugs, as candesartan is metabolized only to a minor extent, with enzyme kinetics characterized by high K_m value. Candesartan can be administered once daily with total daily doses ranging from 8 mg to 32 mg. The usual starting dose of candesartan is 16 mg once daily. Dosage is recommended to be titrated according to the blood pressure response.

Clinical development of candesartan cilexetil is a joint effort involving Takeda, Astra Hässle AB Sweden and Astra Merck Inc.

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BACKGROUND

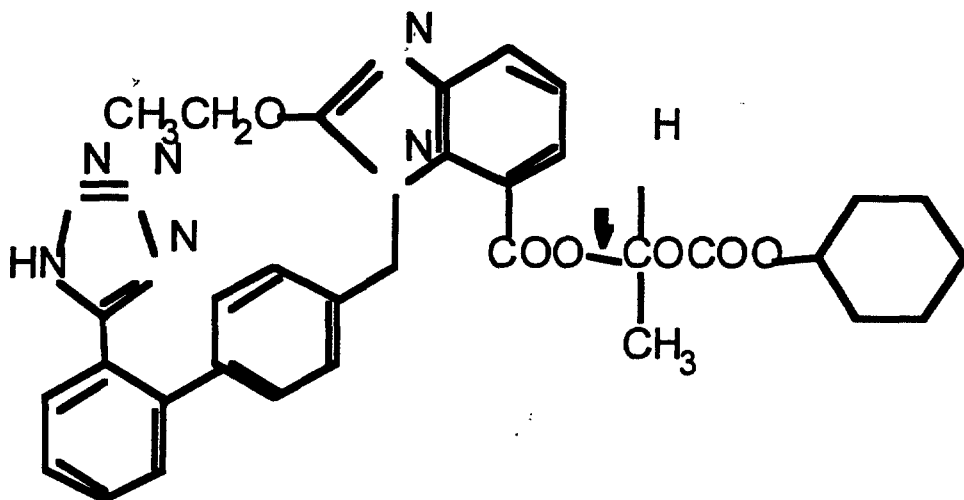
Candesartan cilexetil is a new, potent, orally-active, non-competitive angiotensin II type I selective receptor antagonist. Candesartan exhibited a much greater affinity ($>10,000$ fold) for the AT_1 subtype receptor than for the AT_2 receptor, and a slow rate of dissociation from the AT_1 receptor, *in vitro*.

Esterification of candesartan yields candesartan cilexetil, an inactive, chiral prodrug with markedly improved oral bioavailability compared to candesartan. Candesartan cilexetil is rapidly and completely hydrolyzed to the active drug, candesartan (MI; CV-11974), which itself is achiral, during absorption from the gastrointestinal tract. Candesartan in turn is broken down to an inactive metabolite, MII (CV-15959).

Clinical development of candesartan cilexetil is a joint effort involving Takeda, Astra Hässle AB Sweden and Astra Merck Inc.

DESCRIPTION

Candesartan cilexetil, a nonpeptide, is chemically described as (\pm)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate.



↓ site of ester hydrolysis.

Candesartan cilexetil has a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral. ATACAND will be available for oral use as tablets containing either 4 mg, 8 mg or 16 mg of candesartan cilexetil. Recently, the firm suggested the availability and use of 32 mg tablets. Atacand can be administered once daily with total daily doses ranging from 8 mg to 32 mg.

DRUG FORMULATION: Candesartan Cilexetil tablets are proposed for marketing as circular /biconvex tablets in strength of 4 mg (white), 8 mg (light pink), and 16 mg (pink). Clinical trial formulations were either manufactured by Takeda or Astra (Astra to be marketed). BE study was conducted to compare the two formulations. Detailed composition of the formulations is presented in APPENDIX II.

ANALYTICAL METHODOLOGY: Concentration of candesartan in biological fluids were determined. Overall, the assay methodology as well as its validation was satisfactory. Analytical determinations of candesartan in plasma were obtained. The assay validation of the dissolution methods used by Takeda and Astra was submitted.

Human Pharmacokinetics and Bioavailability Summary

The pharmacokinetics of candesartan after intravenous and oral (solution and tablets) administration have been investigated in healthy adult male volunteers and hypertensive patients, and in special populations (i.e., elderly healthy volunteers, normotensive patients with hepatic impairment and hypertensive patients with renal impairment. Potential food-drug and drug-drug interactions have been investigated in healthy volunteers. The Phase I and IIa studies described in this summary section were performed in Europe, by Takeda Ltd. in collaboration with Astra Hässle AB.

Absorption-Distribution-Metabolism-Excretion

The pharmacokinetics, absolute bioavailability, and excretion pattern of candesartan were determined in eight healthy, young, male volunteers after single doses of 8 mg ¹⁴C-candesartan cilexetil given as an oral alcohol containing solution, and 4 mg ¹⁴C-candesartan administered as a 10 minute I.V. infusion, in an open, randomized, cross-over study with a 3-week wash-out period between investigational days. Blood, urine and feces samples were collected up to 168 hours after drug administration. Plasma was analyzed for candesartan cilexetil, candesartan, and its inactive metabolite CV-15959 (MII).

Pharmacokinetics of Candesartan and its Inactive Metabolite, MII, After Single Doses of 8 mg ¹⁴C-Labeled Candesartan Cilexetil as an Oral Solution and 4 mg ¹⁴C-Labeled Candesartan as a 10-min I.V. Infusion.

Parameter	Candesartan	MI (CV-15959)
Oral administration: mean (SD)		
Absolute bioavailability (%)	42 (6.7)	n.c.
AUC _{0-∞} (ng x h/mL)	1400 (178)	371 (137)
C _{max} (ng/mL)	233 (45.6)	24.0 (10.8)
t _{max} (h)	1.25 (0.46)	4.00 (0.93)
t _{1/2} (h)	9.3 (3.3)	10.4 (2.1)

Parameter*	Candesartan	MII (CV-15959)
Intravenous administration:		
AUC _{0-∞} (ng x h/mL)	2320 (293)	371 (32.7)
C _{max} (ng/mL)	997 (178)	23.7 (5.47)
t _{max} (h)	0.20 (0.04)	4.20 (0.83)
V _{ss} (L/kg)	0.13 (0.02)	n.c.
CL (mL/min/kg)	0.37 (0.06)	n.c.
t _{1/2} (h)	9.7 (3.1)	8.65 (0.62)

1) Absorption

After the oral dose of ¹⁴C-candesartan cilexetil solution approximately 56% of the total radioactivity was absorbed. The average peak plasma concentration (C_{max}) of 233 ng/mL candesartan was reached after 1.25 hours (t_{max}). The absolute bioavailability of candesartan was 42% (based on candesartan solution Vs. IV). Very low plasma concentrations of candesartan cilexetil were detected up to two hours after oral dosing, with a mean C_{max} of 8.6 ng/mL occurring 0.5 hours after drug intake. Candesartan cilexetil in serum was not detected in studies where candesartan cilexetil was administered as tablets in doses of 0.5-16 mg. The relative bioavailability of candesartan tablets compared to oral solution was estimated to be 33.5%

2) Distribution

Candesartan plasma protein binding in vitro was determined to be 99.8%, and candesartan did not penetrate red blood cells. The very high plasma protein binding is consistent with the small apparent volume of distribution at steady state (V_{ss}) of 0.13 L/kg (9 L/70 kg), after I.V. administration, indicating that the distribution of is restricted to that of albumin.

At pH 7 candesartan is ionized (pKa of 3.8 and 2.1) and the partition coefficient between octanol and an aqueous solution is 0.05 at 37°C. This indicates that, at physiological pH, candesartan is relatively non-lipophilic.

3) Metabolism

After both oral and I.V. administration, the major part of the radioactivity, approximately 70-80%, was identified as candesartan, both in urine and feces. The remainder, identified as CV-15959 (MII) is formed by O-de-ethylation. Separate pharmacological and toxicological tests in dogs and rats showed that MII was inactive. Unchanged candesartan cilexetil was not detected in any human urinary or fecal samples after the oral dose.

The metabolism of candesartan by human liver microsomes has been studied in vitro. The formation of MII, the only metabolite found, was catalyzed by isoenzymes within the cytochrome P-450 CYP2C family. The Km and V_{max} for the formation of MII were 376 μmol/L and 511 mg protein/min, respectively. The relatively high Km value makes it unlikely that candesartan inhibits other CYP2C9 mediated reactions in vivo. The plasma concentrations in the therapeutic dose range (C_{max} after a 32 mg dose was about 781 nmol/L i.e. 344 ng/ml which is

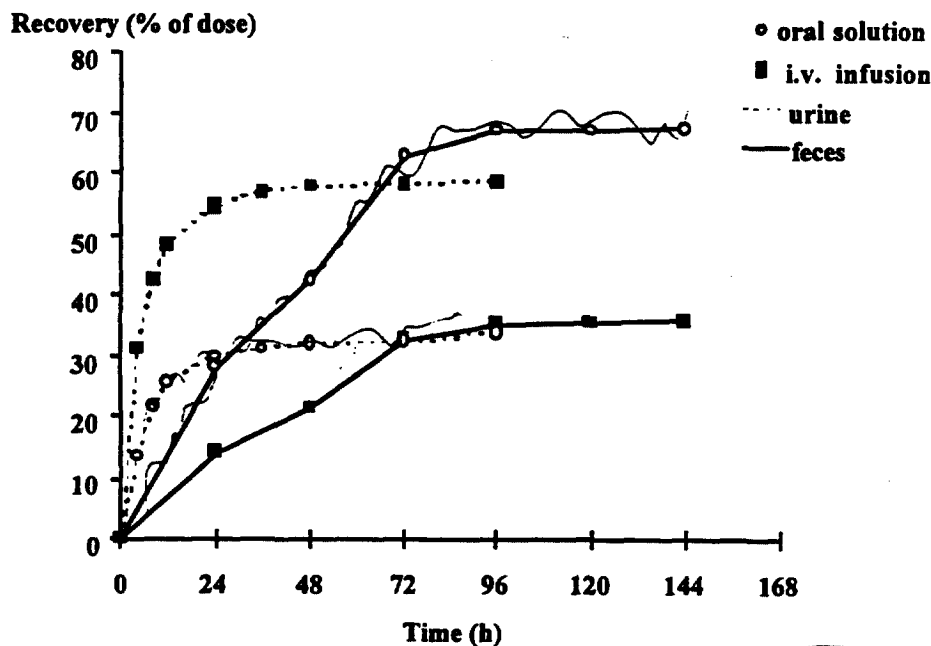
considerably lower than the calculated K_m value of 376 $\mu\text{mol/L}$). This may also indicate that inhibition of the rather limited formation of MII by other drugs, may not cause any significant change in candesartan plasma levels.

Peak plasma concentrations of MII were reached about 4 hours after both oral solution and I.V. administrations. The $\text{AUC}_{0-\infty}$ ratios of MII:candesartan were about 0.16 after I.V. and 0.27 after oral administration.

4) Excretion

Within 72 hours after both oral (solution) and intravenous dosing, >90% of the total radioactivity was excreted, and after 168 hours the recovery was about 100% and 94%, respectively. After oral administration about 33% was excreted in urine and 67% in feces. After I.V. dosing the corresponding values were 59% and 36%, respectively, as depicted in Figure 1.

FIGURE 1
Average Accumulated Recovery of Total Radioactivity (% of Dose) After 8 mg Candesartan Cilexetil p.o. or 4 mg Candesartan I.V. in Urine and Feces.



The fractions of unchanged candesartan excreted in urine were about 0.52 and 0.26, after I.V. and oral doses, respectively. The recovery of candesartan in feces after an I.V. dose indicates biliary excretion. The total clearance (CL) of candesartan determined from the I.V. administration, was 0.37 ± 0.06 mL/min/kg (mean \pm SD), with a renal CL of 0.19 ± 0.03 mL/min/kg (mean \pm SD). The elimination half-life of candesartan was 9.3 ± 3.3 hours (mean \pm SD) after oral administration, similar to that of 9.7 ± 3.1 hours (mean \pm SD) after I.V. administration. The elimination half-life of MII was 10.4 hours and 8.7 hours, after oral and I.V. doses, respectively.

Relative Bioavailability and Bioequivalence

Relative Bioavailability

The relative bioavailability (F_{rel}) of the tablet formulation of 8 mg candesartan cilexetil compared to that of an 8 mg oral solution was 34% (95% CI: 28-40%). The C_{max} was lower (50.9 ng/mL vs. 271 ng/mL), and occurred later (4.3 hours vs. 1.5 hours), after tablet intake compared to the oral solution.

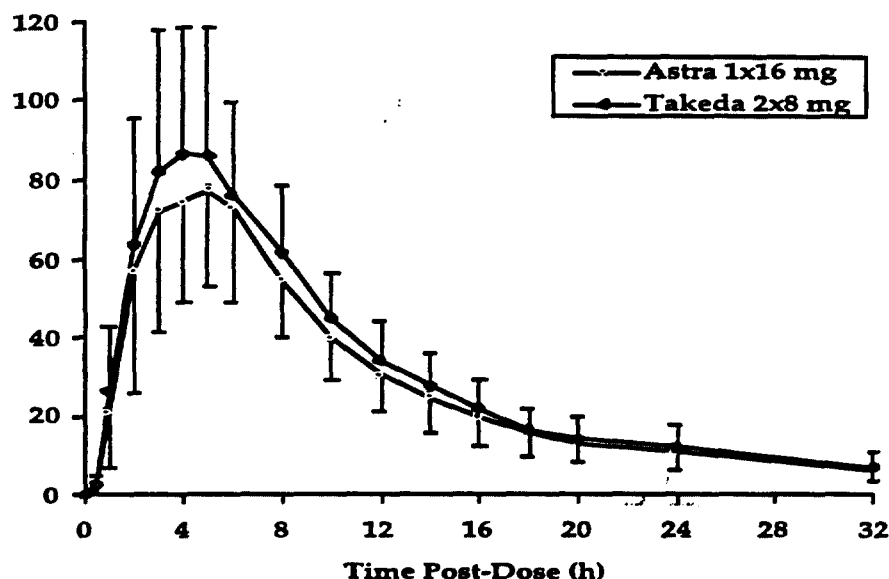
The relatively low bioavailability and slow rate of absorption of the tablet compared to the solution indicate that the dissolution of the substance may be a limiting process for the rate and extent of absorption.

Bioequivalence

Bioequivalence was established between Astra manufactured tablets (test; 1x16 mg) and Takeda manufactured tablets (reference; 2x8 mg). The Astra manufactured tablet is the intended US commercial pharmaceutical formulation. The two tablets are concluded to be bioequivalent since the 90% confidence intervals for the ratio of the true treatment means for C_{max} , $AUC_{0-\infty}$ and AUC_{0-t} were determined to 0.83-1.06, 0.85-0.98 and 0.84-0.97, respectively. The t_{max} and $t_{1/2}$ were similar after the two treatments. The referenced formulation, Takeda manufactured tablets, has been used in most clinical trials. The plasma concentration versus time profiles were comparable between treatments, as shown in Figure 2. For the lower strength tablets (4, 8 mg tablets), in-vitro dissolution were examined and found to be comparable.

FIGURE 2

The Candesartan Plasma Concentration vs. Time Profiles After 16 mg Candesartan Cilexetil Tablets (mean \pm SD; n=28)



Pharmacokinetics After Single and Repeated Tablet Administration

1) Healthy Subjects

Dose proportionality was observed for area under the serum concentration versus time curve (AUC), see Figure 3, and C_{max} after single doses and repeated once daily doses ranging from 2-16 mg. In five different studies the time to reach C_{max} was about 4 hours. The terminal half-life was approximately 9 hours (range 7.7-12.9 hours) in these studies.

The mean fluctuation index during the last dosing interval at steady state, calculated as $(C_{max} - C_{min})/C_{average}$, was consistently in the range of As expected from the half-life of candesartan, there was almost no accumulation after repeated once daily dosing. The mean accumulation factors after different doses ranged between During chronic dosing, estimations of candesartan AUC_t and C_{max} in both healthy subjects and patients were similar in a number of studies.

Serum concentrations of the inactive metabolite of candesartan, MII, were much lower than candesartan and reached peak serum concentrations later, about 4-9 hours after dose intake. The elimination of MII was somewhat slower than that of candesartan, with an accumulation factor of 1.5 after repeated dosing.

2) Patients

The C_{max} and AUC_t of candesartan increased linearly with increasing doses (2-16 mg), both after 4 weeks treatment. The t_{max} and $t_{1/2}$ of candesartan in hypertensive patients and healthy subjects after candesartan cilexetil dosing were also similar. In two small short-term safety and tolerability studies, escalating doses of candesartan cilexetil were given up to 32 and 64 mg. After candesartan cilexetil doses of 4-32 mg and 16-64 mg, the values for AUC_t were consistent with what is expected from the dose linearity seen at lower doses (32 mg: mean AUC_t 2880 ng x h/mL, Day 3; 64 mg: mean AUC_t 4810 ng x h/mL, Day 1).

d. Pharmacokinetics in Special Populations

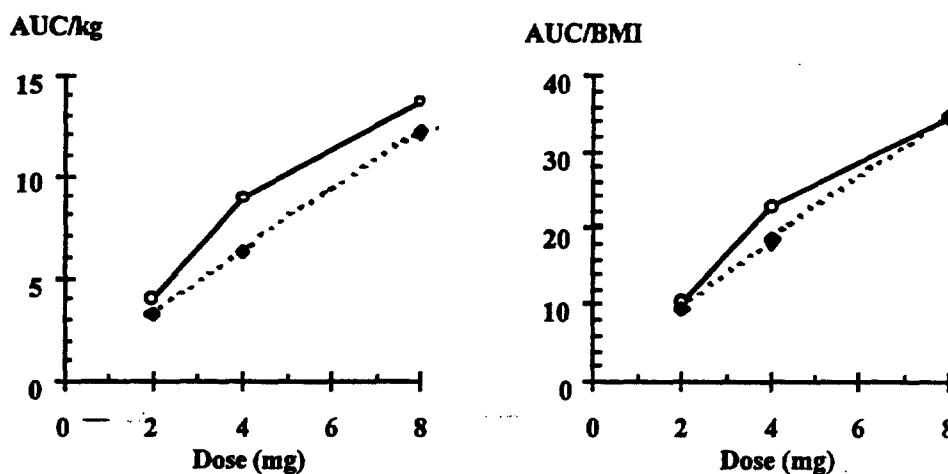
1) Elderly

Candesartan cilexetil was administered in single and repeated doses of 2-16 mg to 33 healthy volunteers of both sexes older than 65 years (range 65-78 years). No accumulation was observed (accumulation factor after seven days repeated dosing. The C_{max} and AUC increased in a dose proportional manner.

Both C_{max} and AUC of candesartan were higher after single and repeated once daily dosing in comparison to younger adult subjects (18-40 years). After repeated AUC_t and C_{max} were higher about 80% and 50%, respectively, compared to the younger adult subjects. No gender related differences were observed after adjustment for body mass index (kg/m^2), as shown in Figure 3.

FIGURE 3

The Influence of Sex on AUC vs. Dose After Correction for Weight (Left Panel) or Body Mass Index (Right Panel); Females (○ ;n=6) and Males (● ;n=8)



The half-life of candesartan in the elderly was somewhat longer (9-12 hours) than in the younger healthy adult volunteers (approximately 9 hours)

2) Normotensive Patients with Impaired Hepatic Function

No differences in the pharmacokinetics or serum protein binding (99.5%) of candesartan were observed between normotensive patients with mild to moderate chronic liver disease (fatty liver or hepatitis; antipyrine CL 10-35 mL/min), and a control group of healthy volunteers, after single and repeated once daily doses for five days of 12 mg candesartan cilexetil. Patients with severe liver impairment have not been studied.

3) Patients with Impaired Renal Function 12 mg candesartan cilexetil was administered in single and repeated once daily doses for five days to 32 (24 evaluable) hypertensive patients with normal kidney function, mild to moderate (CL_{creatinine} 31-60 mL/min/1.73 m²) and severe (CL_{creatinine} 15-30 mL/min/1.73 m²) renal impairment. Increasingly higher C_{max}, greater AUC and a somewhat longer elimination t_{1/2} of candesartan were observed with increasing renal dysfunction, as shown in Table 2. The serum protein binding was decreased in the patients with severe renal impairment (fraction bound 99.2%) compared to those with normal renal function (fraction bound 99.5%).

TABLE 2

Pharmacokinetics of Candesartan After 5 days Repeated Dosing of 12 mg Candesartan Cilexetil Once Daily in Hypertensive Patients with Normal, Mild to Moderate, or Severe Renal Impairment

Parameter	Normal renal function CL _{creatinine} 103 mL/min/1.73 m ² * (n=8)	Mild - moderate renal impairment CL _{creatinine} 45.8 mL/min/1.73 m ² * (n=9)	Severe renal impairment CL _{creatinine} 21.9 mL/min/1.73 m ² * (n=7)
AUC _t * (ng x h/mL)	1062 (812 - 1388)	1600 (1243 - 2060)	2238 (1680 - 2980)
C _{max} * (ng/mL)	106 (87.2 - 130)	151 (125 - 183)	170 (137 - 211)
t _{max} [†] (h)	3.6 (3.0 - 4.3)	3.6 (3.0 - 4.3)	3.3 (2.6 - 4.0)
t _{1/2} ^{†‡} (h)	11.8 (10.0 - 13.7)	12.2 (10.4 - 13.5)	14.3 (12.4 - 16.3)

*geometric mean (90% CI), [†] arithmetic mean (90% CI), [‡] estimate after single dose administration

e. Studies of Potential Interactions

Candesartan is highly protein bound, mainly excreted unchanged via bile and urine, with minor metabolism, solely via cytochrome P450 CYP2C9. The high K_m value (376 μM) makes it unlikely that candesartan inhibits other drugs metabolized by CYP2C9. Furthermore, a change in MII formation rate by other drugs would not significantly affect candesartan plasma levels, since the elimination is only to a minor part dependent on metabolism. The drug-combinations were selected for their likelihood as concomitant therapies, or risk-potential of causing severe adverse reactions.

- Antihypertensives: hydrochlorothiazide (HCTZ) and nifedipine.
- narrow therapeutics: digoxin and warfarin, (the latter also metabolized via cytochrome P450 CYP 2C9 isoenzymes, and extensively bound to serum proteins)
- The highly serum protein bound oral antidiabetic glibenclamide (glyburide)
- typical oral contraceptive (ethinyl estradiol + levonorgestrel), metabolized in the liver

1) Food

The AUC of candesartan after single 8 mg doses of candesartan cilexetil was not altered in 18 healthy male subjects during fed compared to fasting conditions, although there was an increase in C_{max} (26%) and decrease of approximately one hour in t_{max} after a breakfast with high-fat content. This indicates a more rapid rate, but no change in the extent of absorption after food intake.

2) Hydrochlorothiazide

The potential interaction between HCTZ and candesartan after candesartan cilexetil administration was investigated in a double-blind, randomized placebo-controlled, 3-way, cross-

over study. After 7 days repeated once daily dosing of each monotherapy or the combination of 12 mg candesartan cilexetil and 25 mg HCTZ, the AUC_t of candesartan increased by about 20% ($p=0.02$), whereas the AUC_t of HCTZ slightly decreased by 10-15% ($p<0.01$), when the drugs were given concomitantly.

3) Nifedipine

The potential interaction between nifedipine and candesartan after candesartan cilexetil administration was investigated in an open, randomized placebo-controlled 3-way cross-over study. No changes in the pharmacokinetics were observed after the combined 7 days repeated once daily dosing of 16 mg candesartan cilexetil and 30 mg nifedipine as compared to the monotherapies after 7 days repeated once daily dosing of each drug.

4) Digoxin

The study of the potential interaction between digoxin (0.25 mg) and candesartan cilexetil (16 mg) had an open label, randomized, multiple once daily dose, 3-way cross-over design. The pharmacokinetics at steady state after monotherapy of each drug were found to be unaltered compared to that after the combined therapy with candesartan cilexetil and digoxin. Six male and six female healthy volunteers participated in the study. No gender difference was observed after adjusting the pharmacokinetic parameters for body weight.

5) Glibenclamide (Glyburide)

The study of the potential interaction between glibenclamide (glyburide; 3.5 mg) and candesartan cilexetil (16 mg) had an open label, randomized, multiple once daily dose, 3-way cross-over design. The pharmacokinetics at steady state after monotherapy of each drug were found to be unaltered compared to that after the combined therapy with candesartan cilexetil. There was no statistically significant difference of blood glucose levels between combined treatment and glyburide treatment alone, indicating the absence of a pharmacodynamic interaction.

6) Warfarin

The effects of multiple oral doses of 16 mg candesartan cilexetil once daily on the steady state pharmacokinetics and prothrombin time of warfarin were studied in healthy male volunteers. The subjects were administered warfarin once daily in sub-therapeutic doses that produced a prothrombin time (INR) of 1.2-1.8. After approximately two weeks, the subjects took candesartan concomitantly for ten days, and continued with warfarin monotherapy during the last week of the trial. There was a small decrease in trough warfarin serum concentrations during concomitant therapy with candesartan cilexetil, but this decrease was not associated with a decrease in prothrombin time. Therefore dose adjustment of warfarin may not be necessary.

7) Ethinyl estradiol + Levonorgestrel

The pharmacokinetics of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Microgynon® 21) were found to be similar with or without concomitant administration of 8 mg

candesartan cilexetil once daily in a 21-day repeated, cross-over, study in 12 healthy female subjects. The pharmacokinetics of candesartan were similar on days 14 and 21, indicating that this typical oral contraceptive does not influence the disposition of candesartan. The levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), measured on days 7, 14 and 21, were consistently low throughout both investigational periods, indicating that ovulation did not occur during the study.

In conclusion, Candesartan is not likely to be influenced by other drugs, as candesartan is metabolized only to a minor extent, with enzyme kinetics characterized by high K_m and V_{max} values.

General Comments:

1. The pharmacokinetic results of the renal dysfunction study showed higher C_{max} , greater AUC and longer elimination half-lives of candesartan in patients with severe renal dysfunction, as compared to patients with normal renal function. The relevance of these kinetic changes for the clinical use of candesartan cilexetil in patients with severe renal impairment could be evaluated further, based on general risk/benefit considerations, and a validated PK/PD relationship
2. The mechanism of interaction of candesartan and HCTZ was not investigated and still hard to understand. The increase of candesartan bioavailability by about 20% may be insignificant for healthy young population but may result in compounded increase in candesartan concentration in older or renally impaired patients.
3. Although the population analysis found no covariates that significantly affect the clearance of candesartan, it was apparent that age has an effect on CL. Non-linear relationship between age, weight and CL will be investigated in the near future by the reviewer. The use of invalidated version of NONMEM is not usually encouraged.

Labeling Comments:

The information regarding lack of interaction with glibenclamide, nifedipine, digoxin and oral contraceptive in healthy volunteers should be incorporated in the label. The label should also include information on increase in candesartan AUC and C_{max} by approximately 20% with HCTZ, while HCTZ AUC and C_{max} decreased by 14% and 6%. Warfarin levels decreased by about 6% with canesartan.

The firm suggests that no initial dosage adjustment is necessary for elderly patients, for patients with impaired renal function, or for patients with impaired hepatic function. We think for patients with impaired renal function the dose should be initially lower. The same should apply to the elderly specially if treated with diuretics. Details on drug interaction with HCLZ and warfarin should be included in the label, especially in the "PRECAUTIONS" and "DOSAGE AND ADMINISTRATION" sections.

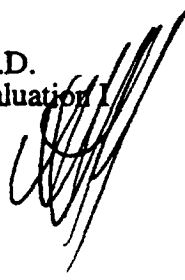
"Absolute bioavailability of candesartan tablet based on data from relative bioavialibilty (tablet vs oral solution is estimated to be 33.5%) should be added to the label at the second paragraph/second sentence of "PHARMACOKINETICS GENERAL".

ATACAND

RECOMMENDATION:

This current submission is acceptable. The dissolution testing on Atacand tablets is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program.

Ahmed El-Tahtawy, R.Ph., Ph.D.
Pharmacokineticist, Pharmaceutical Evaluation I



FT Initialed by A. Parekh, Ph.D. ----- 4/2/98

CC: NDA 20-838

HFD-110

HFD-860 (El-Tahtawy, Malinowski, Parekh)

Chron, Drug, Review Files (CDR, B. Murphy, HFD 870).

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX I

**HUMAN PHARMACOKINETICS AND
BIOAVAILABILITY/BIOEQUIVALENCE
STUDIES**

Study Title : EXCRETION BALANCE AND ABSOLUTE BIOAVAILABILITY STUDY WITH ¹⁴C-LABELLED CANDESARTAN CILEXETIL AFTER A SINGLE ORAL AND INTRAVENOUS DOSE IN HEALTHY MALE VOLUNTEERS
Title (short): Candesartan cilexetil ¹⁴C absolute bioavailability study

Study Code : Sponsor code: SH-AHC-0001
Sponsor : Astra Hässle AB, Sweden
Study director : M. Sunzel, M.Sc., Ph.D.
Investigator

Objectives : - to determine the rates and routes of elimination and the excretion balance of total ¹⁴C-radioactivity after administration of ¹⁴C-labelled candesartan (cilexetil) in man
 - to determine the ratio of ¹⁴C-radioactivity in whole blood and plasma
 - to determine the absolute bioavailability of candesartan cilexetil
 - to assess in vitro plasma protein binding
 - to identify metabolites in plasma, urine and faeces

Design : single dose, open label, randomized, two-period crossover, mass balance and pharmacokinetic study with a washout of three weeks between the drug administrations

Subjects : 8 healthy young male volunteers (two groups of 4 volunteers, separated by one day)

Age : 18-45 yr

Weight : within ± 15% deviation from normal range

Medication 1. : Name : candesartan cilexetil (TCV-116; prodrug)

Active compound : candesartan (CV-11974)

Strength : 0.8 mg.mL⁻¹ candesartan cilexetil

Dose : 8 mg (50 µCi ¹⁴C-radioactivity)

Dosage form : solution for oral administration

2. : Active compound : candesartan

Strength : 0.1 mg.mL⁻¹ candesartan

Dose : 4 mg (50 µCi ¹⁴C-radioactivity)

Dosage form : solution for intravenous infusion

Treatments : single dose administration of ¹⁴C-labelled candesartan (cilexetil) on day 1, after a 10-hour fast

A = oral administration of 8 mg (10 mL) candesartan cilexetil

B = intravenous administration of 4 mg (40 mL) candesartan over 10 minutes

Observation period: each period in clinic from -16 h up to 150 h (afternoon day 7) after drug administration for all subjects, except for Subjects 01 and 07 who left the clinic 174 h after dosing (afternoon day 8) during treatment B; departure from clinic was allowed if the amount of ¹⁴C-radioactivity was less than 75 dpm per mL urine and less than 100 dpm per homogenized faeces sample

Blood sampling: p.o. administration: pre-dose* and 0.5, 1*, 2, 3*, 4*, 5, 6, 8*, 10, 12, 18, 24*, 30, 72, 120 and 168 h post-dose

i.v. administration: pre-dose* and 5, 10*, 15, 20, 30*, 45 min and 1, 1.5, 2*, 3, 3.5, 4*, 4.5, 5, 5.5, 6, 8*, 10, 12, 18, 24, 72, 120 and 168 h after the start of the infusion (* whole blood samples)

Urine sampling: pre-dose (-12-0) and 0-4, 4-8, 8-12, 12-24, 24-36, 36-48 and 24 h post-dose portions thereafter

Faeces sampling: blank and 7 post-dose portions (24-h pools) per subject per period

Bioanalysis : ^{14}C -radioactivity in whole blood, plasma and urine was determined by liquid scintillation counting; in faeces, ^{14}C -radioactivity was determined by combustion followed by liquid scintillation counting. In vitro plasma protein binding of ^{14}C -radioactivity was performed using a Centrifree Micropartition System. Determination of candesartan cilexetil, candesartan and its inactive metabolite CV-15959 in plasma, urine and faeces was performed using liquid chromatography with fluorescence detection

Statistics Pharmacokinetic parameters: for radioactivity, candesartan and MII the following parameters were calculated: C_{\max} , t_{\max} , λ_z , $t_{1/2}$, $\text{AUC}_{0-\infty}$, AUC_{0-x} , A_{faeces}^e (^{14}C only), A_{urine}^e (^{14}C and candesartan only) and A_{total}^e (^{14}C only). For candesartan after i.v. administration V_{ss} , CL and CL_r were calculated and the bioavailability (F) after oral administration was calculated. In addition the ratio whole blood/plasma ^{14}C -radioactivity was calculated. All results were presented descriptively. Primary pharmacokinetic parameters (C_{\max} , $t_{1/2}$, $\text{AUC}_{0-\infty}$ and F) were subjected to ANOVA and 95% confidence intervals were calculated; 95% confidence intervals were calculated for the secondary pharmacokinetic parameters V_{ss} and CL.

Results : Pharmacokinetic parameters: the pharmacokinetic parameters of candesartan after oral and intravenous administration are given below:

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	C_{max} (ng.mL ⁻¹)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng.h ⁻¹ .mL ⁻¹)
8 mg oral ¹⁴ C-candesartan cilexetil				
n	8	8	8	8
mean	233	1.25	9.31	1400
SD	45.6	0.46	3.31	178
min				
max				
geometric mean	229	nc*	8.88	1390
4 mg i.v. ¹⁴ C-candesartan				
n	8	8	8	8
mean	997	0.20	9.71	2320
SD	178	0.04	3.06	293
min				
max				
geometric mean	984	nc*	9.18	2300

* nc = not calculated

After oral administration low concentrations of candesartan cilexetil were seen in plasma during the first two hours. The metabolite of candesartan, MII reached peak plasma concentration between 3 and 5 hours.

The ratios of $AUC_{0-\infty}$ of MII/candesartan were approximately 0.16 after i.v. and 0.27 after oral administration.

The bioavailability after oral administration from dose corrected $AUC_{0-\infty}$ was about 42%.

The total excreted radioactivity was averaging 94% of the dose after intravenous administration and 100% after oral administration and was virtually complete within 72 hours. After intravenous administration approximately 59% was excreted in the urine and 36% in the faeces. After oral administration about 33% was excreted in the urine and 68% in the faeces. The ratio of radioactivity in whole blood versus plasma was on average 0.53 after oral and 0.61 after intravenous administration. The percentage of free drug was 0.16%.

Conclusions : after oral and intravenous administration of ¹⁴C-candesartan (cilexetil), the total recovery of ¹⁴C-radioactivity was virtually complete within 72 hours.

Data on cumulative faecal excretion indicate partly biliary excretion. The ratio of urinary excretion for oral over i.v. (% of dose) indicates an absorption of approximately 56% after oral administration. The bioavailability after oral

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administration calculated from dose corrected $AUC_{0-\infty}$ of candesartan was 42% (95% confidence interval 36-48%).

Metabolic profiling in faeces showed that the drug was excreted as candesartan and MII (88%, and 12%, respectively) which indicates that no other metabolite was formed. The drug did not penetrate into the blood cells and was highly bound to plasma proteins.

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STUDY CODE SH-AHC-0001

5.7. Summary Pharmacokinetic Parameters of Total Radioactivity: Candesartan Cilexetil 8 mg Oral

Analyte		C _{max} (nCi/ml)	t _{max} (h)	λ _z (/h)	t _{1/2} (h)	AUC _{0-∞} (nCi*h/ml)	AUC ₀₋₂₄ (nCi*h/ml)	AUC ₀₋₂₄ /AUC _{0-∞} (%)	Tlin (h)	n
¹⁴ C	N	8	8	5	5	8	5	5	5	5
	MEAN	2.97	1.25	0.0741	9.63	19.7	20.9	95.6	18.00	3.20
	SD	0.499	0.46	0.0147	1.76	2.22	2.14	2.43	0.00	0.447
	MIN									
	MAX									
	GEOMEAN	2.94	nc	nc	9.50	19.6	20.8	nc	nc	nc

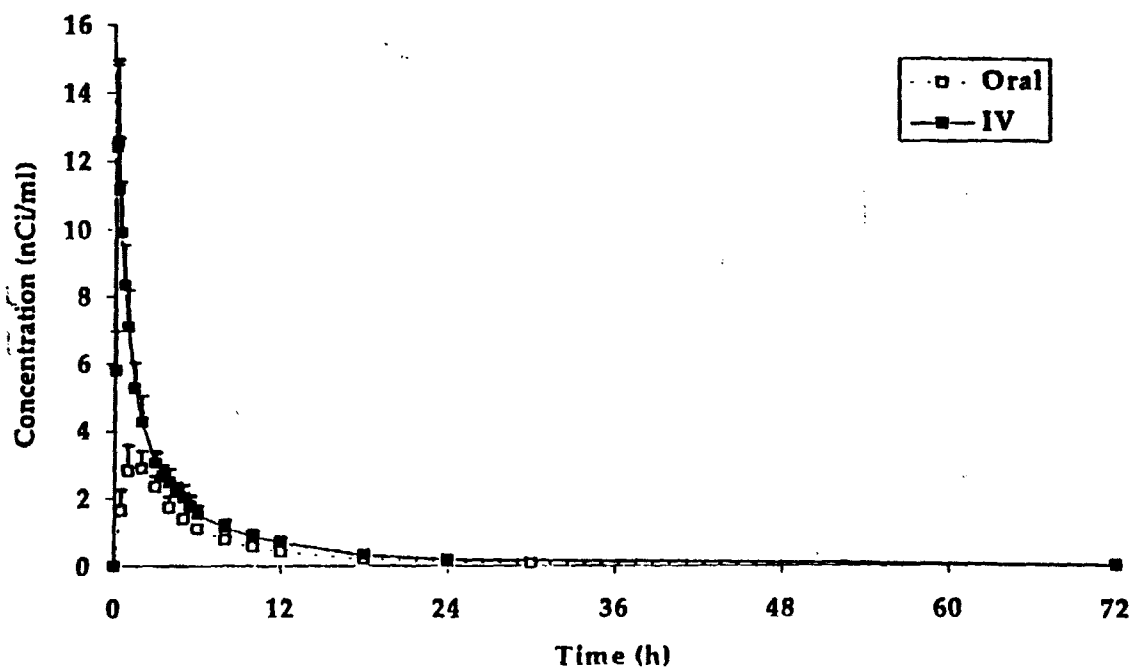
5.8. Summary Pharmacokinetic Parameters of Total Radioactivity: Candesartan 4 mg IV

Analyte		C _{max} (nCi/ml)	t _{max} (h)	λ _z (/h)	t _{1/2} (h)	AUC _{0-∞} (nCi*h/ml)	AUC ₀₋₂₄ (nCi*h/ml)	AUC ₀₋₂₄ /AUC _{0-∞} (%)	Tlin (h)	n
¹⁴ C	N	8	8	5	5	8	5	5	5	5
	MEAN	12.9	0.21	0.0756	9.79	38.4	39.9	98.9	14.80	3.60
	SD	2.34	0.04	0.0244	2.43	5.88	6.56	1.56	4.38	0.894
	MIN									
	MAX									
	GEOMEAN	12.7	nc	nc	9.50	38.0	39.4	nc	nc	nc

nc = not calculated

5. TABLES AND GRAPHS

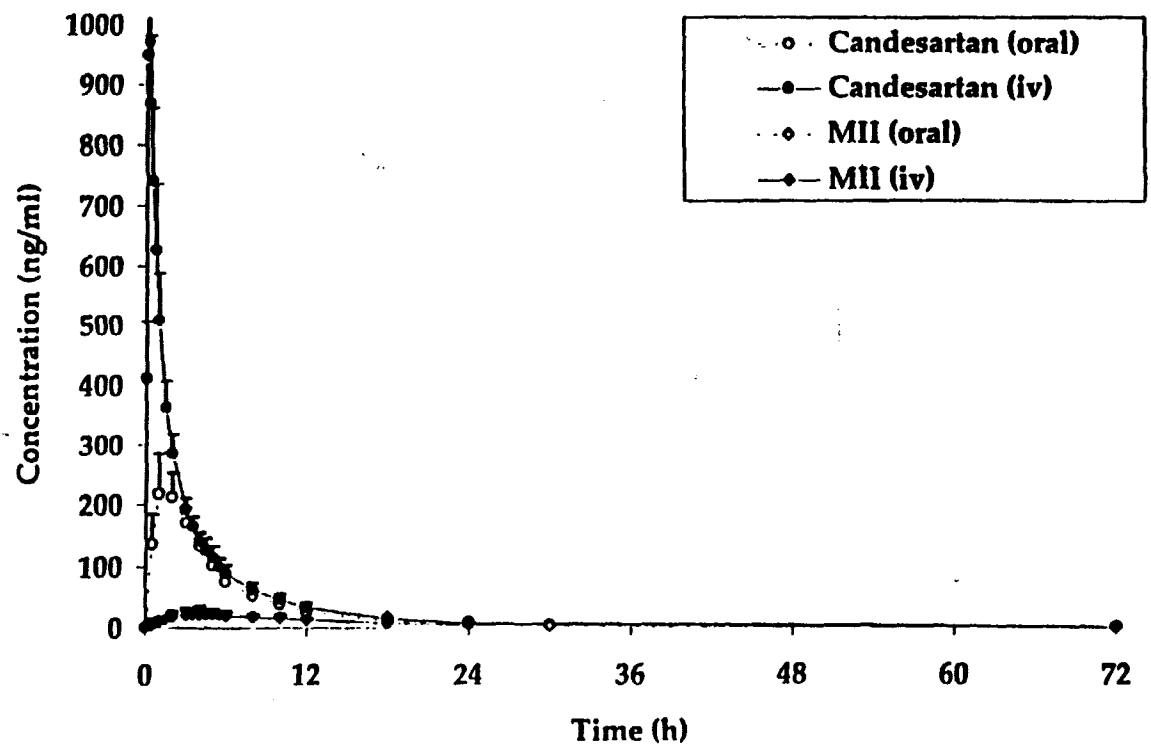
5.1. Mean (+SD) Plasma Profiles of Total Radioactivity: Candesartan Cilexetil 8 mg Oral, Candesartan 4 mg IV, Linear Plasma Concentration Scale



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5.9. Mean (+SD) Plasma Profiles of Candesartan and MII: Candesartan Cilexetil 8 mg Oral, Candesartan 4 mg IV, Linear Plasma Concentration Scale



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Dose-Finding Study of TCV-116 in Patients with Mild to Moderate Essential Hypertension. Double-Blind, Placebo-Controlled, Multiple Dose, Randomized Clinical Trial, Phase II

Investigators:

Study centre(s):

Objectives: The study was performed to compare the blood pressure lowering effect of five different doses (2 mg, 4 mg, 8 mg, 12 mg and 16 mg) of Candesartan cilexetil with placebo in patients with mild to moderate essential hypertension during a treatment period of four weeks in order to find the highest tolerable dose (in the selected dose range), the lowest effective dose and the optimal dose range with regard to efficacy and safety.

Methodology: At specified timepoints blood pressure (BP) was measured three times during a period of five minutes after five minutes' rest in the sitting position. The systolic BP was taken at the appearance of the first audible pulse beat (Korotkoff, Phase I) and the diastolic BP at the disappearance of any audible pulse beat (Korotkoff, Phase V). The arithmetic mean of the last two measurements was used as a reference value. For the BP measurements a recording in steps of 2 mmHg was applied. Blood pressure and pulse measurements were performed at trough, i.e. 24 ± 2 hours after the last drug intake prior to the administration of the next scheduled dose (and just before breakfast).

Study Design: This study was performed in a double-blind, placebo-controlled, multiple dose, randomized fashion on six parallel groups. Following a 2-5 weeks wash-out period, patients underwent a two-week placebo baseline period and then treated with the study drug for a period of four weeks. A one week run-out period followed.

Number of Subjects: 232 in total
(total and for each Treatment) 39 in the 2 mg, 4 mg, 8 mg and placebo group
38 in the 12 mg and 16 mg group

Diagnosis and Criteria for Inclusion: Stable mild to moderate essential hypertension, defined by a (mean) arterial diastolic blood pressure (DBP) in sitting position between inclusively 95 mmHg and 114 mmHg measured at three visits (V 1, V 2 and V 3) during the two weeks of the placebo run-in period

Test Product: TCV-116

Batch No./Doses: Externally indistinguishable Candesartan cilexetil capsules (2 mg, 4 mg, 8 mg, 12 mg and 16 mg), Batch no. E 1160091

Lot No./Doses: Z 5427021 (TCV-116 2 mg), Z 5428021 (TCV-116 4 mg), Z 5429021 (TCV-116 8 mg), Z 5429021 and Z 5428021 (TCV-116 12 mg), Z 5429021 and Z 5429021 (TCV-116 16 mg)

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Duration of Treatment: four weeks

Criteria for Evaluation:

Efficacy: The change of the (mean) sitting diastolic blood pressure (DBP) from baseline (visit 3 in the morning before intake of the last placebo capsule) to the end of the treatment period (visit 9 in the morning, 24 hours after intake of the last capsule of double-blind treatment period before intake of the first placebo capsule of the run-out period) was determined for each patient.

Efficacy Results: Mean diastolic blood pressure decreased dose-dependently from 3.4 mmHg (placebo) to 5.9 mmHg (2 mg) to 6.5 mmHg (4 mg) to 6.9 mmHg (8 mg) to 8.7 mmHg (12 mg) to 8.9 mmHg (16 mg). The differences of the doses 12 mg and 16 mg Candesartan cilexetil vs. placebo were statistically significant. When visit 3 and visit 8 were regarded as baseline and endpoint, respectively, or weighted means of blood pressure measured during 24 hours intervals were compared, all active doses from 4 mg to 16 mg showed statistically significant effects versus placebo.

PK Results

Mean serum concentrations are plotted in Figure 1 and tabulated in Table 11. Concentrations increased with increasing dose in a proportional manner, but there was no accumulation after four weeks of treatment. The accumulation ratio was 1.2-1.4, suggesting that candesartan did not accumulate to a great extent following once-daily dosing for four weeks. This is consistent with the 6-8 hour elimination half-life.

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Table 11

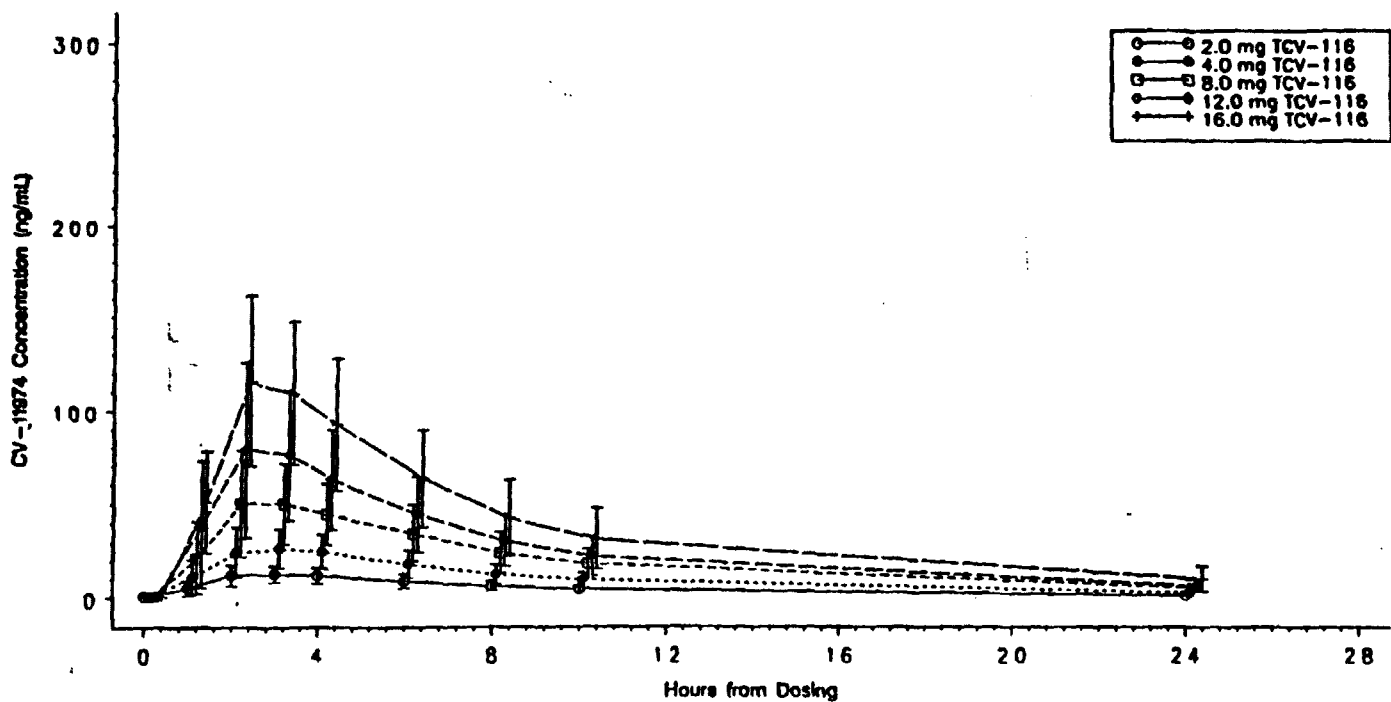
Mean Pharmacokinetic Parameters for Serum TCV-116 Concentrations

Treatment	Visit	Parameter Means						
		C _{max} ng/mL	T _{max} hr	AUC(0-t) ng·hr/mL	AUC(0-24) ng·hr/mL	AUC(0-inf) ng·hr/mL	kel 1/hr	T _{1/2el} hr
2.0 mg	4	14.13	3.1	100.38	107.66	116.27	0.1476	5.86
	8	16.81	3.2	150.44	153.60	175.46	0.1070	7.50
4.0 mg	4	31.73	3.0	244.77	245.85	266.10	0.1171	6.40
	8	32.67	2.9	298.31	299.12	333.88	0.1062	7.18
8.0 mg	4	60.96	2.8	484.43	484.43	530.55	0.1148	6.74
	8	70.99	2.9	611.88	621.16	704.98	0.0931	7.77
12.0 mg	4	88.19	3.0	649.38	652.53	709.45	0.1066	6.78
	8	99.99	2.8	832.69	832.69	929.31	0.1029	7.13
16.0 mg	4	120.58	2.6	931.41	938.20	1036.03	0.1168	6.92
	8	139.44	2.8	1237.71	1237.71	1436.45	0.0909	8.54

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Figure 1
Mean (S.D.) Serum CV-11974 Concentrations Versus Time
Visit 4



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**A RELATIVE BIOAVAILABILITY STUDY OF CANDESARTAN CILEXETIL
COMPARING THE 8 MG PHASE III TABLET FORMULATION WITH AN ORAL
SOLUTION**

INVESTIGATOR:

Dag Elmfeldt, MD, PhD, Astra Hässle AB, S-431 83 Mölndal, Sweden.
Phase I.

OBJECTIVES:

To determine the relative bioavailability of the Phase III tablet formulation (test) of candesartan cilexetil compared to an oral solution (reference).

STUDY DESIGN:

The study was a randomised, open-label, single-dose, two-way crossover investigation in healthy male volunteers, with a wash-out period of at least one week.

NUMBER OF SUBJECTS:

Sixteen subjects entered the study and all completed and were included in the analyses.

DIAGNOSIS AND CRITERIA FOR INCLUSION:

Healthy male volunteers.

INVESTIGATIONAL PRODUCT:

A tablet containing 8 mg candesartan cilexetil, as used in Phase III studies; batch number H 1156-01-01-07 (Takeda batch number Z5429131).

REFERENCE THERAPY:

Oral solution (10 ml) intended to contain 8.0 mg candesartan cilexetil (actually contained 8.1 mg); batch number H 1202-01-01-01.

DURATION OF TREATMENT:

Single dose of each treatment, at least one week apart.

ASSESSMENT METHODS:

Blood samples were drawn for candesartan assay pre-dose and at intervals up to 30 hours post-dose on each study day.

STATISTICAL METHODS:

A mixed effects analysis of variance model was fitted to the logarithmically-transformed estimates of dose-adjusted AUC_{0-∞} values. The least squares estimate for the mean treatment difference (tablet - oral solution) was calculated with 95 % confidence limits on the logged scale, and the anti-logarithms of these values represented an estimate and 95 % confidence interval for

the true mean relative bioavailability. The anti-logarithms of the least squares treatment means were calculated with 95 % confidence intervals (CI).

SUMMARY OF RESULTS:

The estimate of the true mean relative bioavailability of the Phase III, 8 mg tablet compared with an 8 mg dose of oral solution was 33.5% (95% CI: 27.9% to 40.2%). The C_{max} values were lower, and occurred later, with the tablet formulation compared to the oral solution and the apparent half-life was longer following administration of the tablet formulation.

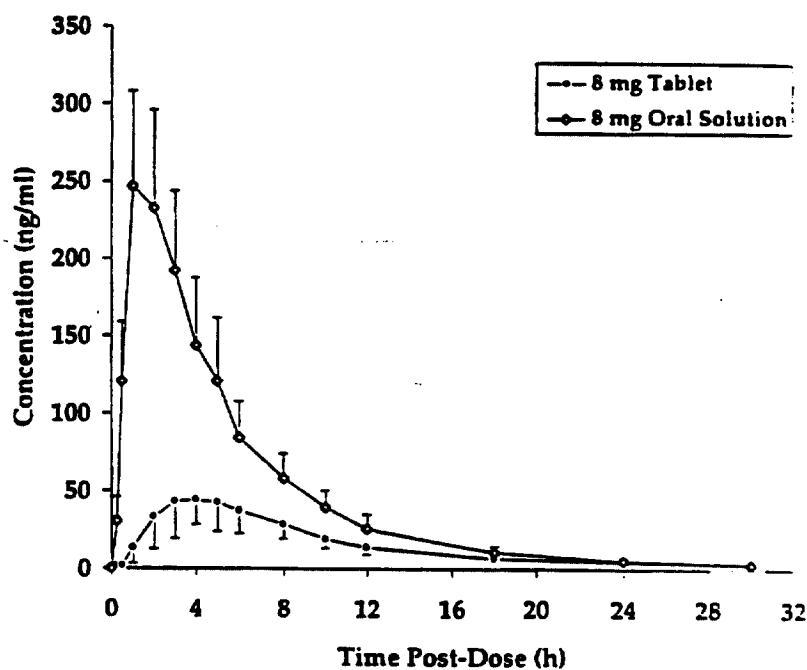
CONCLUSION:

The mean relative bioavailability of the Phase III, 8 mg candesartan cilexetil tablet compared with an 8 mg dose of oral solution was estimated to be 33.5 % (95 % CI: 27.9 % to 40.2 %) after single dose administration.

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STATISTICAL REPORT
STUDY CODE SH-AHC-0005

4.5. Mean (\pm SD) plasma concentration versus time profile
(N=16)



5. CONCLUSIONS

The estimate of mean relative bioavailability of the Phase III, 8 mg tablet compared with an 8 mg dose of oral solution was 33.5 % (95 % CI: 27.9 % to 40.2 %) after single dose administration to healthy volunteers.

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STUDY CODE SH-AHC-0005

4.3.1. MEAN RELATIVE BIOAVAILABILITY
(N=16)

Pharmacokinetic Parameter	Ratio of Anti-logged Least Squares Means 8 mg Tablet/8 mg Oral Solution	95 % Confidence Interval		p-value
		Lower	Upper	
Dose-adjusted AUC _{0-∞} ((ng.h/ml)/mg)	33.5 %	27.9 %	40.2 %	<0.001

The analysis of AUC_{0-∞} was performed on ln-transformed dose-adjusted AUC_{0-∞} values. The ratio of anti-logged least squares $\times 100$ thereby provides an estimate for the true mean relative bioavailability, F_{rel} . A 95 % confidence interval for the true mean relative bioavailability is also presented. The highly statistically significant p-value reflects the large difference in the bioavailability of the two formulations.

The anti-logged least squares means are presented below with 95 % confidence intervals. The anti-logged least squares means are equivalent to the geometric means of dose-adjusted AUC_{0-∞} shown in Section 4.4. (It can be seen that the ratio of $83.3/248.3 \times 100$ is equal to 33.5% as shown above.)

4.3.2. ANTI-LOGGED LEAST SQUARES MEANS
(N=16)

Pharmacokinetic Parameter	Treatment	Anti-logged Least Squares Means	95% Confidence Interval	
			Lower	Upper
Dose-adjusted AUC _{0-∞} ((ng h/ml)/mg)	8 mg Tablet	83.3	72.2	96.1
	8 mg Oral Solution	248.3	215.1	286.5

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STUDY CODE 5H-AHC-0005

4.4. Summary statistics of pharmacokinetic parameters

8 mg Tablet	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-∞} (ng.h/ml)	AUC _{0-t} (ng.h/ml)	t _{1/2} (h)
N	16	16	16	16	16
MEAN	50.9	4.32	501	456	9.19
SD	20.0	1.15	154	148	3.30
MEDIAN	46.9	4.00	500	455	7.86
MIN					
MAX					
CV (%)	39.4	26.7	30.8	32.6	35.9
GEOMETRIC MEAN	47.7	4.18	480	437	8.73
MEAN OF LN	3.86	1.43	6.17	6.08	2.17
SD OF LN	0.367	0.270	0.300	0.300	0.317

8 mg Oral Solution	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-∞} (ng.h/ml)	AUC _{0-t} (ng.h/ml)	t _{1/2} (h)
N	16	16	16	16	16
MEAN	271	1.50	1480	1460	6.21
SD	57.6	0.632	321	316	2.35
MEDIAN	280	1.00	1450	1410	6.00
MIN					
MAX					
CV (%)	21.2	42.2	21.7	21.7	37.8
GEOMETRIC MEAN	265	1.39	1450	1420	5.96
MEAN OF LN	5.58	0.329	7.28	7.26	1.78
SD OF LN	0.231	0.397	0.224	0.224	0.269

Summary Statistic	Dose-adjusted AUC _{0-∞} (ng.h/ml)/mg 8 mg Tablet	Dose-adjusted AUC _{0-∞} (ng.h/ml)/mg 8 mg Oral Solution	F _{rel} (%)
N	16	16	16
MEAN	86.8	254	35.3
SD	26.8	55.0	11.3
MEDIAN	86.7	249	33.4
MIN			
MAX			
CV (%)	30.8	21.7	31.9
GEOMETRIC MEAN	83.3	248	33.5
MEAN OF LN	4.42	5.51	3.51
SD OF LN	0.300	0.224	0.339

**A SINGLE DOSE BIOEQUIVALENCE STUDY OF CANDESARTAN CILEXETIL
COMPARING 1x16 MG WITH 2x8 MG TABLET(S)**

INVESTIGATOR:

Dag Elmfeldt, MD, PhD, Astra Hässle AB, S-431 83 Mölndal, Sweden.
Phase I.

OBJECTIVES:

To show whether or not one 16 mg immediate release (IR) tablet (Astra) and two 8 mg IR tablets (Takeda) were bioequivalent in healthy subjects after single oral doses.

STUDY DESIGN:

The study was a randomised, open-label, single-dose, two-way crossover investigation. There was a wash-out period of at least one week between doses.

NUMBER OF SUBJECTS:

In total, 29 subjects entered the study and 28, aged between 20 and 39 years, completed. One subject was withdrawn as he was found to be ineligible.

DIAGNOSIS AND CRITERIA FOR INCLUSION:

Healthy male subjects giving written informed consent.

INVESTIGATIONAL PRODUCT:

1x16 mg candesartan cilexetil IR tablet manufactured by Astra Production Tablets AB, Sweden; batch number H 1191-01-01-01.

REFERENCE THERAPY:

2x8 mg candesartan cilexetil IR tablets manufactured by Takeda Chemical Industries Ltd, Japan; batch number H 1156-01-01-02 (Takeda batch number Z5429081).

DURATION OF TREATMENT:

Single dose (16 mg) of each treatment.

ASSESSMENT METHODS:

Plasma candesartan concentrations were measured up to 32 hours post-dose.

STATISTICAL METHODS:

The least squares estimate for the mean treatment difference was calculated with 90 % confidence limits after fitting a mixed effects analysis of variance model to each of the logarithmically-transformed parameters, AUC_{0-∞}, AUC_{0-t} and C_{max}. The anti-logarithm of the estimate and 90 % confidence limits represent an estimate and 90 % confidence interval (CI) for the ratio of true treatment means.

SUMMARY OF RESULTS:

For AUC0-∞, AUC0-t and Cmax, the 90 % CIs for the ratio of true treatment means were 0.85-0.98, 0.84-0.97 and 0.83-1.06, respectively. AUC0-∞ and AUC0-t were slightly, but statistically significantly ($p=0.048$ and 0.029 , respectively), smaller with the Astra tablet, but there was no difference in Cmax between the formulations. As the CIs lie within the defined interval 0.80-1.25, the two formulations are concluded to be bioequivalent for all three variables. Both formulations were well tolerated.

CONCLUSION:

The 16 mg IR tablet (Astra) is bioequivalent to two 8 mg IR tablets (Takeda) after single dose administration to healthy male subjects, with respect to AUC0-∞, AUC0-t and Cmax.

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STUDY CODE SH-AHC-0004

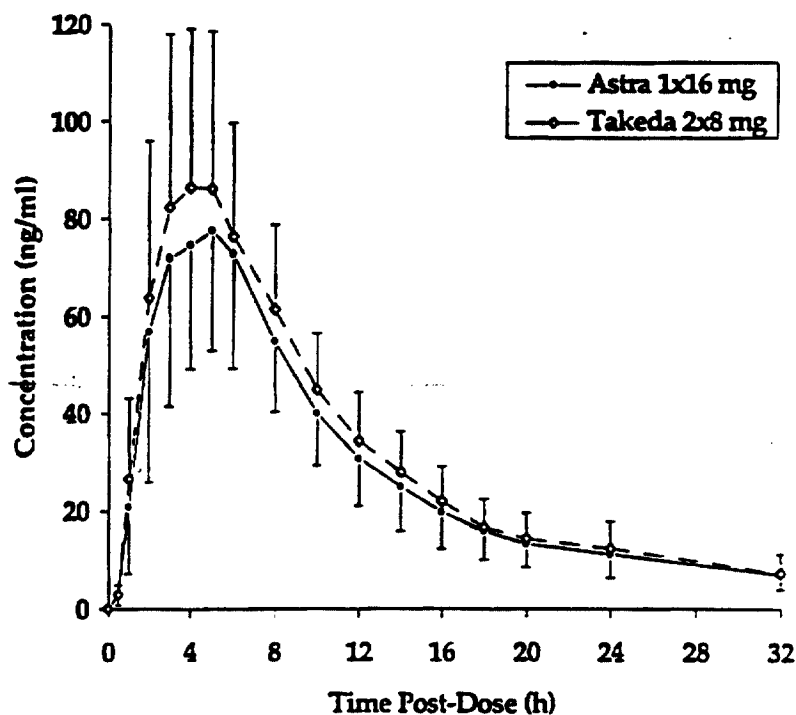


Figure 2. Mean (\pm SD) plasma candesartan concentration versus time profile (N=28).

Plasma candesartan concentrations were above the limit of quantitation of the assay up to 32 hours post-dose in all subjects.

Pharmacokinetic parameters of candesartan were established for each subject following single oral administration of Astra 1x16 mg and Takeda 2x8 mg tablet(s). Estimates of the true treatment medians for AUC and C_{max} are presented in Table 1 and the least squares estimates and 90 % CI for the ratio of the true treatment means (AUC and C_{max}) are shown in Table 2. Summary statistics for the pharmacokinetic parameters are given in Table 3. Individual subject data are presented in Appendix 3 (Statistical Report Appendix).

A common T_{lin} of 12 hours was selected as the point to start the linear regression for determination of λ , and related parameters in all subjects.

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STUDY CODE SH-AHC-0004

The 90 % CI for the ratio of true treatment means were 0.85-0.98 for $AUC_{0-\infty}$, 0.84-0.97 for AUC_{0-t} , and 0.83-1.06 for C_{max} . The pharmacokinetic parameters t_{max} and $t_{1/2}$ were similar for the two treatments.

Table 1. Least squares estimates and 95 % confidence intervals for the true treatment medians (N=28).

Pharmacokinetic Parameter	Tablet	Anti-logged Least Squares Mean	95% Confidence Interval	
			Lower	Upper
$AUC_{0-\infty}$ (ng.h/ml)	Astra 1x16 mg	989	911	1073
	Takeda 2x8 mg	1083	997	1176
AUC_{0-t}^* (ng.h/ml)	Astra 1x16 mg	891	818	971
	Takeda 2x8 mg	987	906	1076
C_{max} (ng/ml)	Astra 1x16 mg	82.9	72.3	95.0
	Takeda 2x8 mg	88.3	77.0	101.2

* t = 32 h in all subjects

Table 2. Least squares estimates and 90 % confidence intervals for the ratio (1x16 mg/2x8 mg) of the true treatment means, presented with p-values (N=28).

Pharmacokinetic Parameter	Estimate	90% CI		p-value
		Lower	Upper	
$AUC_{0-\infty}$ (ng.h/ml)	0.91	0.85	0.98	0.048
AUC_{0-t}^* (ng.h/ml)	0.90	0.84	0.97	0.029
C_{max} (ng/ml)	0.94	0.83	1.06	0.370

* t = 32 h in all subjects

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A Phase One, Double Blind, Randomized, Placebo Controlled, Multiple Dose, Crossover Study in Healthy Elderly Volunteers, to Investigate the Pharmacokinetics, Pharmacodynamics and Safety of a New Antihypertensive Agent; Candesartan Cilexetil (TCV-116)

Investigator:

Study Center:

Objectives: To investigate the pharmacokinetics, pharmacodynamics, and safety of single and multiple doses of orally administered candesartan cilexetil in elderly, healthy, Caucasian subjects of both gender.

Methodology: Randomized, placebo controlled, single and multiple dose, crossover study

Number of Subjects (planned and analyzed): Twenty-one subjects were enrolled in the study (8 females and 13 males) and 18 completed the study according to the protocol (8 females and 10 males). Of the three subjects dropped, two were replaced. The subjects who completed the study were included in the efficacy and pharmacokinetic analyses, and the data from all subjects who enrolled in the study were used for safety analysis and tolerance evaluation.

Diagnosis and main criteria for inclusion: Healthy male and female volunteers aged 65-85; body weight within $\pm 15\%$ of normal body weight range; having given written informed consent.

Test Product, dose and mode of administration, batch number, lot number:

Candesartan cilexetil; 2.0 mg, 4.0 mg, and 8.0 mg tablets; Batch number E1160211; Lot number Z5427021 (2.0 mg); Lot number Z5428021 (4.0 mg); and Lot number Z5429021 (8.0 mg)

Reference Preparation, dose, and mode of administration, batch number, lot number:

Placebo tablet, Batch number E1160211; Lot number Z5425021

Duration of treatment: Single and multiple oral dose; three dosing periods; four possible treatments (three test products and placebo); each subject was exposed to active drug at all test periods or placebo at all test periods. There was a seven day washout between doses.

Name of Active Ingredient: Candesartan Cilexetil (TCV-116), absorbed as the metabolite CV-11974 (active)

Criteria for evaluation:

Pharmacodynamics: Plasma renin activity, aldosterone, angiotensin I and II, angiotensin-converting-enzyme

Pharmacokinetics: Blood analysis for candesartan cilexetil, CV-11974, and CV15959. Urine analysis for CV-11974 and CV-15959.

Safety: Physical examination, clinical laboratory tests, vital signs, continuous cardiac monitoring for 24 hours postdosing, adverse events

Statistical methods: Analysis of variance and regression methods were used to analyze pharmacokinetic and pharmacodynamic variables.

SUMMARY - CONCLUSIONS

PHARMACODYNAMIC AND PHARMACOKINETIC RESULTS:

Blood pressure and pulse values remained relatively constant over the dosing periods. There were increases in Angiotensin (AI, AII), and plasma renin activity (PRA) that may be attributable to administration of candesartan cilexetil. This was supported by the results of the combined PK/PD modeling. There was little accumulation of CV-11974 after seven days of once-daily dosing. On Day 1, mean CV-11974 C_{max} values for the 2.0, 4.0, and 8.0 mg dose levels were 21.8, 42.3, and 83.8 ng/mL, respectively. On Day 9, mean C_{max} values for the 2.0, 4.0, and 8.0 mg dose levels were 25.6, 49.2, and 78.4 ng/mL, respectively. On Day 1, mean AUC(0-24) values for the 2.0, 4.0, and 8.0 mg dose levels were 209, 424, and 867 ng*hr/mL, respectively. On Day 9, mean AUC(0-24) values for the 2.0, 4.0, and 8.0 mg dose levels were 245, 498, and 850 ng*hr/mL, respectively. Neither T_{max} nor half-life appeared to change with dose level or after multiple dosing. Mean T_{max} values ranged from 3.7 to 4.5 hours and mean half-life values ranged from 7.2 to 9.7 hours.

SAFETY RESULTS:

Neither serious nor severe adverse events were observed. All adverse events were of a mild intensity. The most common adverse event reported was "headache".

CONCLUSION:

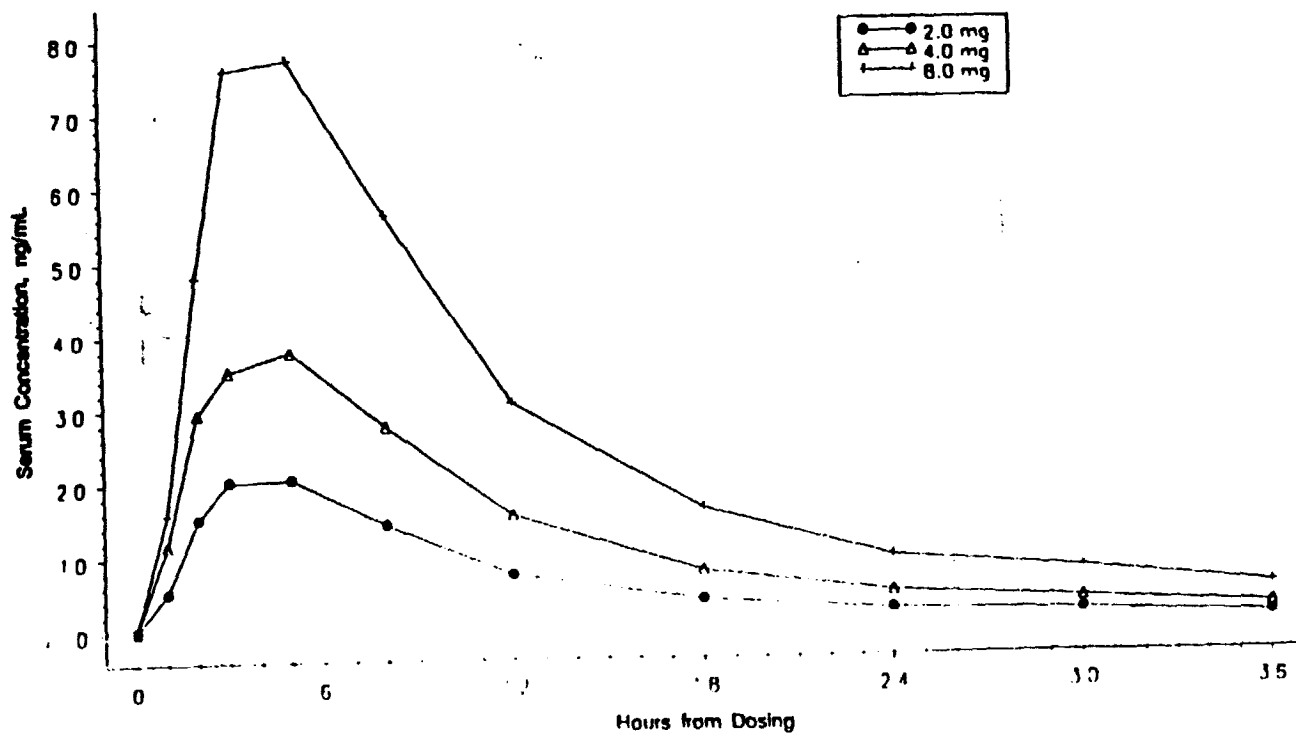
Doses of 2.0, 4.0, and 8.0 mg candesartan cilexetil were found to be well tolerated when administered in multiple doses to healthy, elderly subjects.

Blood pressure and pulse values remained relatively constant and did not appear to be significantly altered by administration of candesartan cilexetil.

Concentrations of CV-11974 were greater in these elderly subjects than observed for younger subjects in a previous study using the same dose levels, resulting in greater C_{max} and AUC values in the elderly subjects. This appeared to be due to slower elimination of CV-11974 in the elderly subjects.

The pharmacokinetics of CV-11974 were well characterized by a biexponential disposition model with zero-order input. AI, AII, and PRA concentrations increased following administration of candesartan cilexetil, though these values were smaller than previously observed in younger subjects.

Figure 4.1
Serum CV-11974 Concentration versus Time - Day 1
(Mean at Each Time)

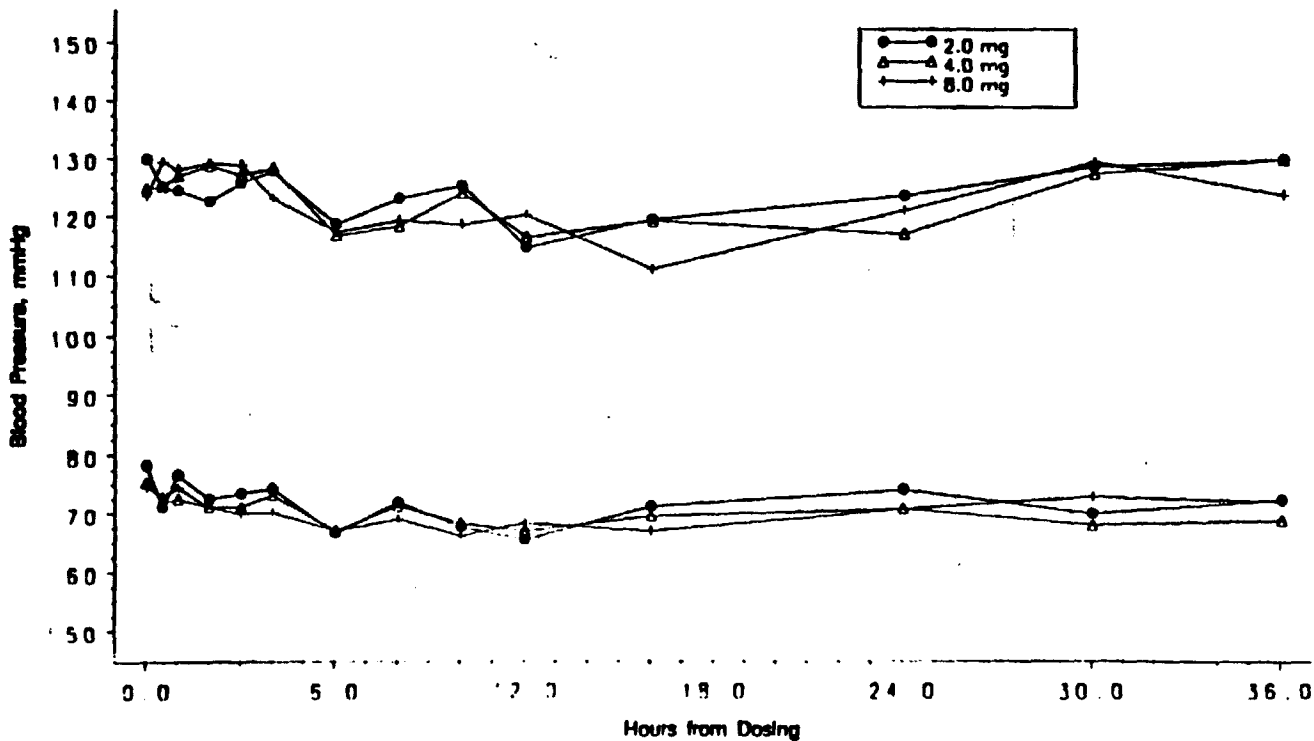


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Figure 2.1

Supine Blood Pressure versus Time Following TCV-116
(Mean Systolic and Diastolic Blood Pressure at Each Time on Day 1)



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Table 5.11.2
Serum CV-11974 Non-Compartmental Pharmacokinetic Parameters by Gender - Day 1
Mean (Standard Deviation)

Dose Level	Gender	N	C _{max} (ng/mL)	T _{max} (hour)	AUC (ng·hr/mL)	AUC _{INF} (ng·hr/mL)	MRT (hour)	KE _L (1/hour)	t _{1/2} (hour)
2.0 mg	Female	6	23.66 (7.86)	4.0 (1.1)	222.49 (64.83)	250.95 (62.19)	11.43 (3.25)	0.1030 (0.0273)	7.29 (2.59)
	Male	8	20.33 (4.52)	3.5 (0.9)	199.14 (46.07)	228.27 (46.94)	11.54 (1.34)	0.0988 (0.0133)	7.13 (1.04)
4.0 mg	Female	6	46.60 (13.50)	4.0 (1.1)	468.30 (142.66)	542.56 (158.61)	11.62 (1.35)	0.0909 (0.0113)	7.72 (0.94)
	Male	8	39.09 (9.49)	4.5 (1.9)	391.29 (64.80)	448.76 (68.27)	12.19 (2.68)	0.0908 (0.0137)	7.81 (1.34)
8.0 mg	Female	6	85.13 (25.68)	4.0 (1.1)	936.39 (234.99)	1087.5 (260.32)	12.33 (1.84)	0.0891 (0.0118)	7.89 (1.06)
	Male	8	82.85 (22.21)	4.3 (1.0)	812.60 (228.92)	953.76 (273.35)	12.45 (2.32)	0.0849 (0.0116)	8.30 (1.19)

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Pharmacokinetics, renal hemodynamic effects and safety of treatment with 12 mg CANDESARTAN CILEXETIL once daily in hypertensive patients with normal renal function or with mild to moderate and severe renal dysfunction.

Investigator:

Study centre(s):

Objectives: To characterize and compare the single and multiple dose kinetics of CV-11974 (active metabolite of CANDESARTAN CILEXETIL) following CANDESARTAN CILEXETIL administration to hypertensive patients with normal renal function or with different degrees of renal dysfunction. Further the tolerability and the course with time of blood pressure were to be assessed.

Diagnosis and main criteria for inclusion: Male or female hypertensive patients with a diastolic BP ≥ 90 mmHg and ≤ 109 mmHg, between 18 and 65 years of age. Groups with a creatinine clearance (Cl_{creat}) > 60 ml/min/1.73 m² BS, Cl_{creat} between 31 - 60 ml/min/1.73 m² BS and Cl_{creat} between 15 - 30 ml/min/1.73 m² BS, respectively.

Methodology: 8 patients with $Cl_{creat} > 60$ ml/min/1.73 m² BS (group A), 9 patients with Cl_{creat} between 31 - 60 ml/min/1.73 m² BS (group B) and 7 patients with Cl_{creat} between 15 - 30 ml/min/1.73 m² BS (group C) received 12 mg CANDESARTAN CILEXETIL once daily on day 1 and on days 3 to 7, immediately prior to a light breakfast. Blood for serum pharmacokinetics and protein binding determination of Candesartan (CV-11974) was collected predose and up to 48 hours after dosing on day 1 and up to 216 hours after dosing on day 7. Fractionated inulin and PAH clearances during 3 hours were measured on day -1 (baseline) and on day 7, to calculate glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively.

Please refer to the attached list of abbreviations.

Number of patients	Planned:	Enrolled:	Evaluable for pharmaco-kinetics:	Evaluable for pharmaco-dynamics:
	24	32	24	24
	(8 pts/group)			

Test product, dose and mode of administration, batch number (study medication), lot number (bulk tablets): CANDESARTAN CILEXETIL 12 mg tablets p.o., once daily
Batch no.: E1160411 (Lot no.: Z542 B041) and Batch no. E1160412 (Lot no.: Z542 B061)

Duration of treatment: Once daily doses on day 1 and on days 3 to 7

Evaluation Criteria Please refer to attached list of abbreviations

ATACAND

- Pharmacokinetics:** C_{max} , t_{max} , AUC_{tau} , $AUC_{0-\infty}$, $t_{1/2}$, R_{ac} , R_{kin} , f_u
- Pharmacodynamics:** Renal Hemodynamics: Inulin clearance as measure for glomerular filtration rate (GFR), PAH clearance as measure for effective renal plasma flow (ERPF)
- Statistical Methods:** Descriptive statistics (mean, SD, median, 90 % confidence interval for the mean) and an analysis of variance (ANOVA) for pharmacokinetic and pharmacodynamic parameters.

Pharmacokinetic Results:

The arithmetic means (SD) of terminal elimination half-lives (h) of CV-11974 in groups A, B and C, respectively, were 11.8 (2.9), 12.2 (2.9) and 14.3 (3.3) on day 1, and 12.3 (0.96), 17.3 (8.8) and 20.7 (7.2) on day 7. The half-lives became longer with increasing renal dysfunction.

The geometric means (SD) of C_{max} -values (ng/ml) in groups A, B and C were 109 (34), 161 (63) and 147 (13) on day 1, and 106 (26), 151 (55) and 170 (67) on day 7. C_{max} in groups B and C were significantly higher than in group A.

AUC increased with increasing renal dysfunction, the geometric means (SD) of $AUC_{0-\infty}$ (ng*h/ml) in groups A, B and C, respectively, were 1209 (440), 1926 (1184) and 2280 (418) on day 1, and 1373 (660), 2465 (1524) and 3905 (1000) on day 7. The corresponding values for AUC_{tau} (ng*h/ml) after repeated doses were 1062, 1600 and 2238 on day 7. The differences between groups were significant on both day 1 and on day 7.

The factor R_{kin} , which describes changes in oral clearance, was not different from unity in either group. The geometric mean of the accumulation factor R_{ac} was 1.14 in group A, 1.28 in group B and 1.71 in group C, showing, as consequence of the longer elimination half-life, a more pronounced accumulation in patients with severe renal dysfunction. The mean t_{max} were around 4 h and did not differ between groups.

Serum Protein Binding Results:

There was no change between day 1 and day 7 in free fraction of CV-11974 in either group. After pooling results of day 1 and day 7 of each group the geometric means of the free fraction (% of total serum concentration) were 0.55, 0.70 and 0.77 in group A, group B and group C, respectively, indicating an increase of free fraction in patients with mild-to-moderate and severe renal dysfunction, as compared to patients with normal renal function.

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Pharmacodynamic
Results:

There were no differences between the groups for any of the renal parameters: GFR calculated as inulin clearance, ERPF calculated as PAH clearance. After pooling of groups the geometric means (90% confidence interval) of fractional changes (ratio day 7/day -1) were 1.16 (1.09 - 1.23) for PAH clearance, and 0.99 (0.92 - 1.07) for inulin clearance, thus indicating a statistically significant increase between day -1 (baseline) and day 7 of 16 % in effective renal plasma flow (PAH clearance), without any change in glomerular filtration rate (inulin clearance). The administration of candesartan cilexetil had only a minor effect on the GFR when compared to baseline prior to CANDESARTAN CILEXETIL treatment. Either in patients with normal renal function or in those with different degrees of renal insufficiency GFR remained stable, whereas most patients showed a consistent increase in ERPF after receiving candesartan cilexetil which was significant in groups A and C. As a result of the effect on renal hemodynamics filtration fraction (FF) fell significantly after candesartan cilexetil administration reaching statistical significance in group C when comparing FF day 1 with day 7.

Conclusion:

The pharmacokinetic results of this study showed higher C_{max} , greater AUC and longer elimination half-lives of CV-11974 in patients with severe renal dysfunction, as compared to patients with normal renal function.

The relevance of these kinetic changes for the clinical use of candesartan cilexetil in patients with renal impairment has to be evaluated further, based on general risk/benefit considerations, and a validated PK/PD relationship.

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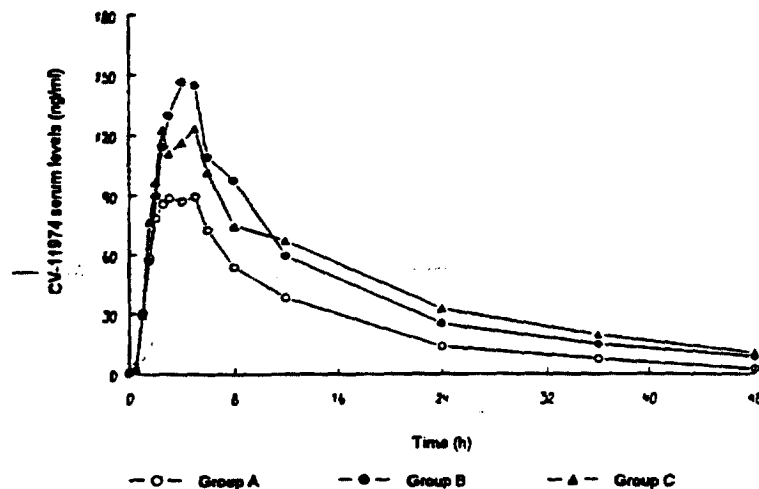
3 LIST OF ABBREVIATIONS

ACE	=	Angiotensin converting enzyme
AE	=	Adverse event
AT I	=	Angiotensin I
AUC ₀₋₁	=	Area under the serum concentration-time curve from zero until last measured concentration.
AUC _{0-∞}	=	Area under the serum concentration-time curve from time zero until time infinity
AUC _{tau}	=	Area under the serum concentration-time curve during one dose interval (tau)
AUMC	=	Area under the serum concentration • time-time curve
blq	=	Below limit of quantitation
BP	=	Blood pressure
C _{av}	=	Average serum concentration (trough)
CI	=	Confidence interval
Cl _{creat}	=	Creatinine clearance
C _{max}	=	Peak serum concentration
C _{last}	=	Last measurable serum concentration
C _{min}	=	Minimum serum concentration
CRF	=	Case report forms
CV-11974	=	Candesartan
CV-15959	=	Pharmacologically inactive metabolite of CV-11974
f _L	=	Fraction of CV-11974 not bound to serum proteins
ECG	=	Electrocardiogram
ERPF	=	Effective renal plasma flow
FF	=	Filtration fraction
GFR	=	Glomerular filtration rate
MRT	=	Mean residence time
PAH	=	Para-amino hippurate

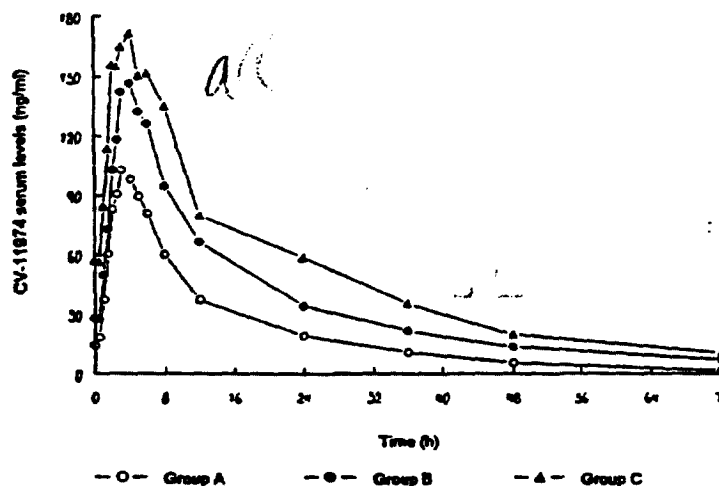
PTF	=	Peak-trough fluctuation
PTS	=	Peak-trough swing
R_{ac}	=	Accumulation factor: $AUC_{0-\infty}(\text{day 7})/AUC_{0-\infty}(\text{day 1})$
R_{kin}	=	Factor: $AUC_{0-\infty}(\text{day 7})/AUC_{0-\infty}(\text{day 1})$
RAS	=	Renin-angiotensin system
SAE	=	Serious adverse event
SD	=	Standard deviation
τ	=	Dosing interval
t_{max}	=	Time of peak concentration
$t_{1/2}$	=	Elimination half-life
WIC	=	Written informed consent

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T-Figure 1a: Mean candesartan serum concentration - time courses following dosing on study day 1 of patients with normal renal function (group A, n=8), patients with mild renal dysfunction (group B, n=9) and patients with severe renal dysfunction (group C, n=7). Linear scale.



T-Fig. 1b: Mean candesartan serum concentration - time courses following dosing on study day 7 of patients with normal renal function (group A, n=8), patients with mild renal dysfunction (group B, n=9) and patients with severe renal dysfunction (group C, n=7). Linear scale.



9.5. FIGURES

Figure E-1: Mean candesartan serum concentration - time courses following dosing on study day 1 of patients with normal renal function (group A, n=8), patients with mild renal dysfunction (group B, n=9) and patients with severe renal dysfunction (group C, n=7). Logarithmic scale.

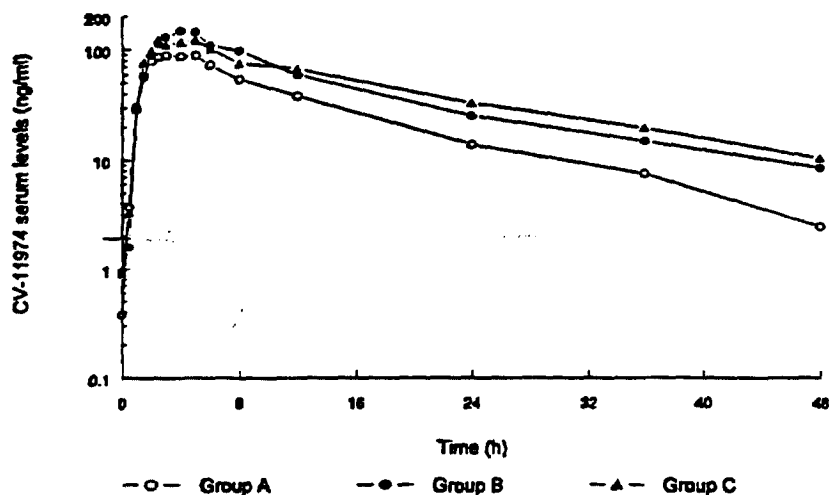


Figure E-2: Mean candesartan serum concentration - time courses following dosing on study day 7 of patients with normal renal function (group A, n=8), patients with mild renal dysfunction (group B, n=9) and patients with severe renal dysfunction (group C, n=7). Logarithmic scale.

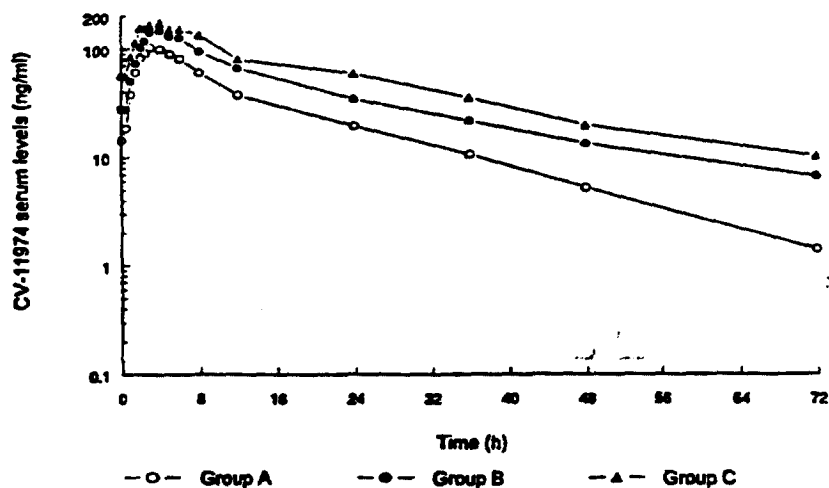


Figure E-34: Mean (SD) diastolic blood pressure (DBP) on days 1 to 10

